REMARKS

Reconsideration and withdrawal of the rejection with respect to all of the claims now in the application, i.e., namely claims 34 to 43, is respectfully requested in view of the foregoing amendments and the following remarks.

Initially, Applicants wish to thank the Examiner for his courtesy in granting the personal interview to the inventors and their attorney on December 6, 2000. Although no agreement was reached at such time, Applicants wish to thank the Examiner for his suggestions in amending the claims to better distinguish over the prior art of record.

The Examiner will recall that during the interview, Applicants explained the invention having regard to two different immunological pathways: what Applicants termed an IgE independent pathway and an IgE dependent pathway. In *in vitro* studies, such as performed by Applicants, an IgE dependent response occurs when a cell, or cell-line, is exposed to a sensitizing agent, typically serum containing IgE from a sensitized individual, whereas an IgE independent response occurs in the absence of said sensitizing agent, or serum. The two pathways are closely related and, indeed, our results indicate that activation of the IgE independent pathway can subsequently, in the presence of pre-allergen (see below), lead to activation of the second IgE dependent pathway.

Notably also, the cell-mediators that are released during the IgE independent response (il4 and il13) bring about IgE isotype switching and so are likely to favor activation of the IgE dependent response.

Thus, it is the interplay between these two pathways that has lead to development of the present invention.

During the course of Applicant's research, it was discovered that substances that cause IgE independent cell mediator release from cells, or cell-lines, of mast cell or basophil lineage can go on to produce a full-blown IgE mediated allergic response. Applicant's considered these substances as potential allergens, hence the use of this term in original claim 16. (Pre-allergen is another term that Applicant's have used to describe these substances.)

Thus, Applicants have invented a method for identifying a class of substances (or pre-allergens) that, using conventional assay techniques, were not thought to be allergenic.

In the exemplary work described in the patent application, Applicants used a mast cell line termed RBL-2H3. These cells or clones and their production are described in detail on page 2 of the patent specification. The data described in Figures 1-4 and tables 1 and 2 was derived using this material. Figure 1 shows the IgE dependent release of cell mediators from human and rat derived clones. Figure 2 shows the IgE dependent release of

two different cell mediators from a human derived clone. Figure 3 is essentially the same as 2, except serum was used as the sensitizing agent. Figure 4 uses the same human clone as before, but in this case cells were challenged with allergen in the absence of presence of sensitising agent (in this case serum). The results clearly show that the cells Applicants used were able to produce mediator release in either case. Notably, the nature of the mediator release was different but, nevertheless, a response was obtained in both instances. Similarly, in table 2, there is described cell mediator release from Applicants' clones in the absence of sensitizing agent.

The above data clearly shows the use of cells that are capable of releasing cell-mediators in the absence or presence of a sensitizing agent. The description of the results repeats this information again and again, both in terms of the titles used to describe the figures and tables and in the discussions thereof. From reading this patent, one would understand from the content of the document, both explicitly - having regard to the words used - and implicitly, that Applicants were using a cell-line that was capable of an IgE dependent and an IgE independent response. (If not Applicants would not have been able to obtain the data). Accordingly, it is respectfully submitted that there is sufficient basis for the introduction in new claim 34 (old claim 16) of a reference to such a cell-line, using words that are used throughout

the specification when describing the cell-line and the way it responds to allergen.

The Examiner will note that new claim 34 (old claim 16) has been amended by the deletion of the term "potential irritancy" thus overcoming any outstanding objections vis a vis the right to priority and by the inclusion, in subsection a., of the phrase "wherein said cell-line is capable of releasing cell-mediators in the absence or presence of an immunoglobulin sensitizing agent such that substance, if an allergen, is capable of activating immunoglobulin dependent or immunoglobulin independent release of said cell mediators depending upon the nature of the allergen".

Furthermore, old claim 17 has been deleted and new dependent claims 35 and 36 have been added. Old claims 18-24 have been renumbered as Claims 37-43 and amended accordingly. Claims 25-30 and 31-33 have been deleted.

Turning now to the prior art relied upon by the Examiner, in general it is respectfully submitted that, the Examiner is arguing with hindsight, and the arguments in support of his rejection are either invalid or if valid, the publications in fact teach away from the invention rather than suggesting the invention to one skilled in the art.

More particularly, on page five of the Office Action, the Examiner states that Cantor et al. teach methods for the determining the allergic status of an individual that uses mast

cell lines (correct), while Gilfillan et al. teach that RBL-2H3 cell line transfected with alpha chain of hFceR1 can be sensitized via exposure to hIgE (correct) and Levi-Schaffer and Bochner et al. teach that mast cell activation results in the release of mediators that cause the signs and symptoms of the allergic response (incorrect) and that mast cells respond to IgE dependent and IgE independent activators (correct), while etc.

Levi-Schaffer explicitly states on the quoted page (p. 308) "On the other hand IgE independent stimulation causes preferential release of histamine without the synthesis of leukotrienes or prostaglandins."

We are clearly looking at a different mechanism. If there are no leukotrienes and prostaglandins, are we going to get a clinical response, or will it be subclinical, and if its subclinical is it allergic?

Thus, Levi-Schaffer teaches that IgE independent mast call response does not lead to a conventional "allergic" response, if any response at all, and therefore:

1. The Examiner's argument is not valid and/or;

2. It would not be obvious to use an IgE independent assay to test for allergenicity. Indeed, the Levi-Schaffer data would teach against it, rather teaching the use of a clinical assay in order to get a clinical response.

Insofar as the Komisar et al. and Bochner publications are concerned, the former relates to toxic shock, the latter anaphylactic shock (possibly synonymous?); in any event, both are extreme and highly distinguishable allergic responses. It's not appropriate or valid to take documents concerning the extreme workings of the immune system and apply them to a common assay system. For instance, Applicants plan to test anything and everything with their screening system i.e., lots of things to which we are daily exposed without suffering toxic shock or anaphylaxis. These references could be said to be "specialized papers", and one cannot fairly extrapolate their content to "lesser" immune responses of the sort Applicants are likely to be screening for. In any event, they take us no farther than Levi-Schaffer, because they do not go on to distinguish the nature of the mediators released. They simply assume that, because of the clinical condition, the IgE independent mechanism is the same as, or at least ultimately produces the same effect as, the IgE dependent. For all we know, the IgE independent mechanism, in the absence of other mechanisms, may not produce any allergic response.

Indeed, if it were obvious to do so, why hasn't it been done before? If it really is such an obvious assay, given the appreciable value, its simplicity of use, the increasing legislation regarding toxic substances etc., why, if the prior art really is pointing in the direction of our invention, has no one

done it yet? Why has Applicants findings and work in this field been published in prestigious scientific journals? The answer is simple, this is an unobvious improvement over the prior art and it is only through hindsight reasoning in light of Applicant's disclosure that can such a reconstruction of the prior art be made and this is, of course, patently improper.

Finally, Applicant hereby requests a one month extension of time in which to respond to the outstanding Office Action. A check in the amount of $55.00 is enclosed herewith for the official fee associated therewith. In the event of any deficiency for the required amount for an extension of time, please debit Deposit Account No. 07-0130.

In view of the foregoing, it is respectfully submitted that the claims are patentably distinguishable over the art of record. Accordingly, reconsideration and withdrawal of the rejection and allowance of the claims are earnestly solicited.

Respectfully submitted,

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